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INFORMATION FOR PRESCRIBERS

EXABLATE VERSION 2.46

ExAblate 2000

Magnetic Resonance guided Focused Ultrasound Surgery

PUB 240013
Information for Prescribers
2004 November

InSightec • ExAblate® 2000 System
Revised 08 November 2004

Information for Prescribers

Caution	FEDERAL LAW RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A PHYSICIAN TRAINED IN MRI AND WHO HAS COMPLETED TRAINING IN THE USE OF THE DEVICE.

Read all instructions, including CONTRAINDICATIONS, WARNINGS and PRECAUTIONS, prior to use. Failure to follow these instructions could result in serious patient injury.
Specialized training in both magnetic resonance imaging and use of the ExAblate are critical to ensure proper performance and safe use of this device.

Physicians should contact their local InSightec representative prior to initial use of the ExAblate to obtain information about training and receive the required certification. Collaboration with a physician trained in gynecology for patient evaluation is strongly recommended.

Note For an explanation of ExAblate specific terms used in this document, please refer to the Glossary at Appendix 1.

DEVICE DESCRIPTION

Overview

The ExAblate 2000 System is a device that can target and ablate uterine fibroid tissue without requiring a surgical incision, using a technique called magnetic resonance image guided focused ultrasound surgery (MRgFUS), illustrated in **Figure 1.** The ExAblate combines two key technological features: (1) a *focused ultrasound beam* that can heat and ablate the tissue within the body while minimizing the risk of damaging the tissue along the beam path; and (2) a *magnetic resonance (MR) imaging and thermal mapping system*, which permits visualization of the patient anatomy for treatment planning, and quantitative information on the change in tissue temperature to monitor and control the treatment.

The ExAblate treatment uses *ultrasound* energy to heat the fibroid to the point of thermal ablation (the heating of tissue to a temperature resulting in the killing of the cells). Similar to the way a magnifying glass focuses light; ultrasound waves are directed through the patient's abdomen and into the fibroid.

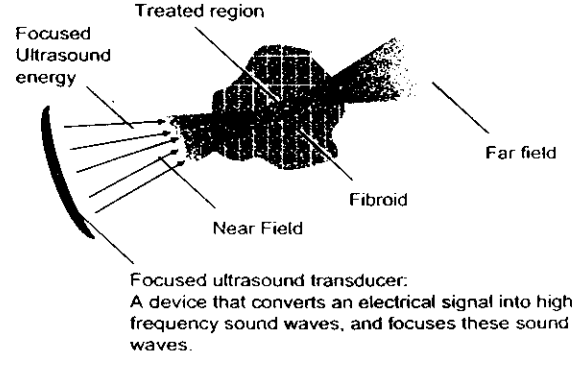


Figure 1 How Focused Ultrasound Works

As shown in **Figure 1**, the *treated region* of tissue is generated in a manner similar to the way a magnifying glass focuses light. The ultrasound waves are focused into a maximum volume approximately 12 x12 x 30 mm (sonication size can be changed by the physician). The ablation of each focal volume of tissue is described as a *sonication*. The ultrasound waves cause a rapid temperature rise at the focal point sufficient to achieve thermal ablation. The tight focusing of the ExAblate is designed to limit the ablation to the targeted region and minimize the heating of tissue outside the target.

As the treatment is performed, the *MR thermal mapping system* displays the change in tissue temperature as an overlay on the anatomic image, creating a thermal "map" that changes over time as the tissue is heated, then cools.

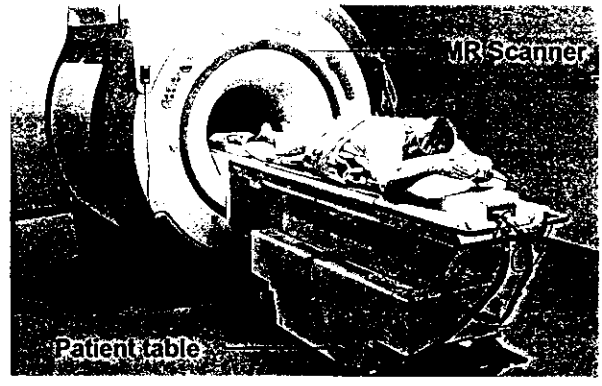
The hardware and software components of the ExAblate are described below.

Hardware

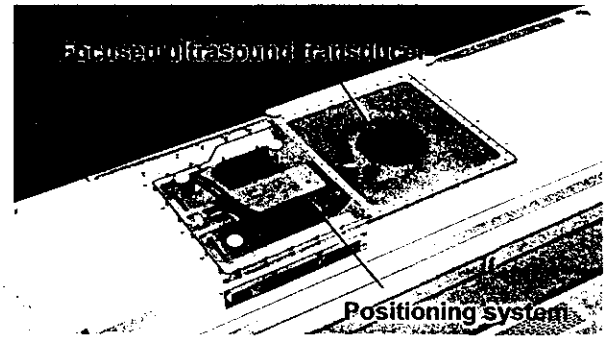
The ExAblate is comprised of three main hardware components:

- Patient Table
- Workstation
- Equipment Cabinet

The Patient Table is what the patient lies on during the treatment. The table docks onto an existing MR system. The table consists of the patient cradle and the base. The cradle, which slides in and out of the MR magnet bore, consists of a water bath which houses the phased array focused ultrasound transducer. The transducer is connected to a positioning system, also located in the cradle. The base consists of electronic components used to generate focused ultrasound, such as transducer power modules and control cards. The patient table is connected to the equipment cabinet. The Patient Table is shown in **Figure 2**.



The patient table docks to the MR scanner



The patient table also houses the focused ultrasound transducer and positioning system

Figure 2 ExAblate Patient Table

The Workstation is what the physician uses to plan and control the treatment. It consists of a PC with a screen, mouse and keyboard. Also part of the workstation is the Stop Sonication Button, used to immediately terminate electrical power to the transducer in case of emergency. The workstation is connected via a data-switching hub to the MR-computer.

The Equipment Cabinet, usually located in an equipment room behind the MR, consists of additional electronics, amplifiers and power supplies. It includes a computer that receives instructions from the physician workstation, processes and executes them, translates them into physical system operations (e.g., begin sonication, end sonication, move transducer, execute Stop Sonication), and communicates with the MR system.

During treatment, the Workstation retrieves planning images and phase images from the MR-computer. The Workstation's graphical user interface overlays icons and colors on the MR images for treatment planning and evaluation. It is on the Workstation that the physician sets treatment parameters (such as power, duration, and spot size) and monitors acoustic reflection and cavitation during sonication.

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Software

The ExAblate software allows the physician to plan and execute the treatment using a graphical user interface. The software steps the physician through each stage of the treatment planning.

These steps to complete a treatment are as follows:

- **Calibration** is the first stage of any ExAblate treatment session. This stage provides the system with the necessary information to correlate patient position, MR scan plane and therapy transducer location.

- **Load Data** is the second stage. This stage transfers the images from the MR system to the ExAblate for treatment planning.

- **Draw** stage provides many tools with which to plan the course of a therapy session. This process begins with the definition of the region of treatment (ROT), skin line, tissue contours, and the selection of a specific treatment protocol.

- **Plan** stage is where the system automatically creates a treatment plan based on the ROT prescribed and treatment protocol selected.

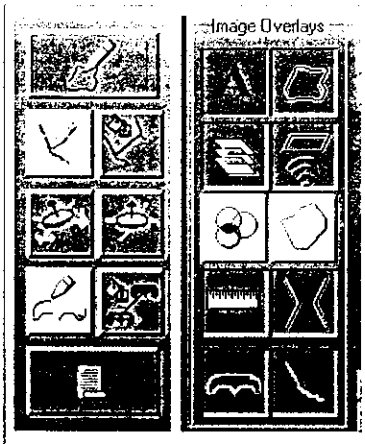
- **Verify** stage includes the confirmation of the geometrical and dosimetry aspects of the treatment.

- **Treat** stage is the actual delivery of energy to each of the planned locations for ablation of the planned region of treatment.

  For more detailed information about each of these functions, refer to the ExAblate Operator's Manual, Chapter 5.

Graphical User Interface (GUI)

The GUI, shown in **Figure 3**, was designed to be physician friendly, using mostly buttons, icons, graphical representations and annotations and overlays directly on the MR image. For example, the skin line, region of treatment, individual sonications and beam passzone are overlaid on MR images in three planes. Most of the treatment operations can be performed using the mouse with minimal manual data entry.



Graphical user interface uses buttons and icons to identify functions during treatment planning.

The software overlays graphical displays on the MR image, as exemplified by the beam path and sonication in this image.

Figure 3 ExAblate Software Graphical User Interface

Dialogue boxes and tool tips that appear when the cursor hovers over a button assist the user at every stage.

- **Image acquisition**

  The software communicates with the MR-computer software to acquire planning images, and MR phase images during treatment.

- **Imaging tools**

  Image enhancing operations, such as zoom in/out, image contrast and measurement tools, can be used on MR images during the treatment planning and delivery.

- **Safety mechanisms**

  Safety mechanisms are built into the software preventing the physician from bypassing steps necessary for a safe treatment. For example, the skin line must be drawn before the system can create a sonication plan, and fiducial markers denoting anatomical structures must be placed before verification of treatment geometry and dosimetry.

- **Sonication parameters and status**

  Treatment parameters are set using pre-planned protocols. Within a limited range, the physician can adjust to the energy level, sonication and cooling duration, spot size, mode type and ultrasound frequency prior to each sonication. The software also keeps track of the status of each sonication (including energy delivered, elapsed time, and thermal dose volume).

- **Cavitation / reflection monitoring**

  During treatment, the software displays the reflection monitoring graph and cavitation spectrum to the physician.

- **Thermal mapping**

  The software uses the MR images to calculate thermal maps. It then displays this thermal map as an overlay on the anatomic images. This provides both quantitative (± 10° C) feedback, in the form of a time/temperature graph, and qualitative feedback, as a color map, to assist the physician in the management of the treatment. The software also displays which regions are calculated to have exceeded the theoretical thermal dose required to cause necrosis. For a more complete discussion of the physics and accuracy of thermal imaging, please see references [1-10]. A more detailed explanation of this feature is provided in the Operator's Manual (see pages 65-66).

Patient Treatment Kit

In addition to the hardware and software, an individual patient treatment kit, shown in **Figure 4** is also required for use of the ExAblate.

This kit is comprised of:

- 1 Acoustic gel coupling pad
- 1 1-Liter bottle of degassed water
- 1 Drape
- 1 Scraper
- 1 20-mL packet of ultrasound gel

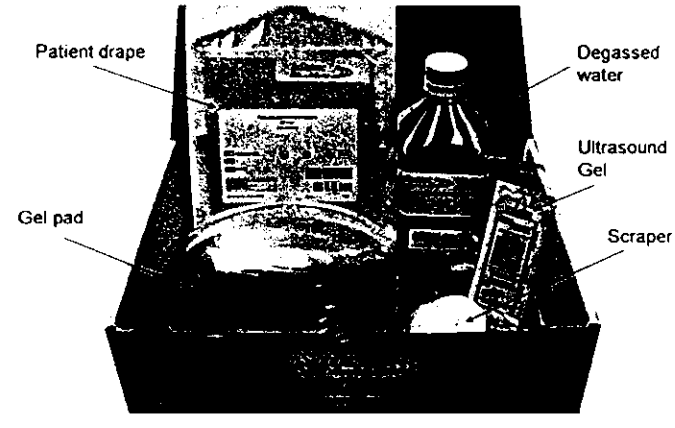


Figure 4 ExAblate Patient Use Kit

INTENDED USE / INDICATIONS FOR USE

The ExAblate 2000 System is intended to ablate uterine fibroid tissue in pre- or peri-menopausal women with symptomatic uterine fibroids who desire a uterine sparing procedure. Patients must have a uterine size of less than 24 weeks and have completed child bearing.

PATIENT/FIBROID SELECTION CRITERIA FOR TREATMENT WITH EXABLATE

Patient Selection Criteria

- Definitive diagnosis of a uterine fibroids as the source of symptoms
- Able to fit into MRI unit
- Able to tolerate the procedure with conscious sedation or no sedation; does not require general anesthesia
- Able to communicate sensations to the physician during the procedure
- Able to activate "Stop Sonication" button

CONTRAINDICATIONS

- The ExAblate treatment is contraindicated for use in women with MRI related issues (e.g., presence of metallic implants that are incompatible with MRI and sensitivity to MRI contrast agents).

- Do not perform the ExAblate procedure if you are unable to remove important structures (e.g., scar, skin fold or irregularity, bowel, pubic bone, IUD, surgical clips, or any hard implants) from the path of the ultrasound beam.

WARNINGS

- You must stop the procedure if:
  - manipulation of the beam fails to achieve a clear path to the targeted fibroid, or
  - the 'ROT' cannot be placed ≥15-mm from the serosal lining in all planes.

- Prolonged immobilization may lead to increased risk of deep venous thrombosis (DVT) or pulmonary embolism (PE). The duration of the sonication portion of the treatment should be limited to 180 minutes.

- The non-perfused volume of fibroid tissue following ExAblate treatment may be greater than the volume targeted for treatment.

- To reduce the risk of thermal damage to tissue beyond the fibroid capsule, including structures in the far field of the focused ultrasound path, the following restrictions on the ExAblate procedure should be observed:
  - The maximum volume of an individual fibroid to be sonicated should not exceed 50%
  - When targeting a volume of fibroid, ensure that no portion of the targeted volume is within 15 mm of uterine serosa
  - When the sacrum or other bony structure is in the far field of the beam path; ensure that it is more than 4 cm from the center of the focus
  - If the sacral nerve is in the far field of the beam path, use one or more of the following techniques to minimize the risk of nerve heating or damage to the sacral nerve:
    - Use Pitch to increase incidence angle of the beam path with sacrum
    - Modify the sonication [use Roll, move laterally; move anterior; choose shorter spot length; delete spot] so the nerve is not in the far field
    - Choose a higher sonication frequency
  - If the patient complains of any nerve stimulation when the sacral nerve is in the far field, immediately change the treatment plan.

- No more than 2 treatments should be performed within a 2 week period.

- Women who are pregnant or desire to become pregnant in the future should not have the ExAblate treatment. Pregnancies following ExAblate could be dangerous for both mother and fetus.

- The transducer interface (gel pad and water) must be in complete contact with the patient's abdomen without gaps to avoid skin burns. Monitor the display throughout treatment for skin folds, bubbles or loss of complete contact between the gel pad and the skin to avoid possible burns.

- Ensure that the patient can activate the Stop Sonication Button before initiating treatment. In the event of pain or patient motion, failure to do so may result in serious injury.

- Accurate calibration of the alignment of the transducer at the start of the treatment is critical to proper tissue targeting and to avoid injury to non-targeted tissue. Perform geometrical and dose verification prior to treatment to ensure proper alignment before beginning treatment.

- Cavitation and reflection can result in serious injury to non-targeted tissue. Both reflection and cavitation should be constantly monitored throughout the treatment.

- Failure to monitor the MR thermal map during the procedure may result in unintended heating of non-targeted tissues, which may cause permanent injury. Cancel/abort the procedure if MR thermometry data are not available.

- Failure to evaluate the ultrasound beam path prior to each sonication from the skin line in the near field through the extent of the far field can result in energy delivery to critical structures anywhere along the beam path that can be painful or cause serious injury. Prior to the delivery of the first sonication and throughout the treatment, the beam path should be evaluated to avoid:
    - Abdominal scars or other irregularities in the skin which can cause pain or skin burns.
    - Loops of bowel in the beam path anterior to the uterus which could become heated to the point of thermal damage.
    - Sonications closer than 15 mm from the serosal surface of the uterus which could cause damage to the muscular wall of the uterus or adjacent bowel.
    - Bones such as the sacrum which may differentially absorb heat that could damage adjacent structures, including nerves. If the sacrum is in the far field of the beam path, no sonication should be performed within 4 cm of a bony structure in the far field of the beam. The angle of incidence of the beam on the sacrum should be as high as possible, ideally greater than 30°.
    - Nerves (e.g., sacral nerve) in the far field. Nerves in the far field can absorb heat from the adjacent bone or fat that can result in nerve injury. If the sacral nerve is in the far field for one or more sonications, change the tilt of the transducer to move the far field off of the nerve or increase the angle of incidence with the sacrum. If the patient complains of any nerve stimulation when the sacral nerve is in the far field, change the treatment plan to move or delete the sonication.

- Inadequate cooling time between sonications could lead to thermal build-up that may cause serious damage to normal tissues outside the targeted volume. The cooling time between sonications should NOT be decreased

below the 90 second default except in very limited circumstances (for example, during the Verify Stage when low power sonications are being used).

Refer to the Operator's Manual for the ExAblate and the GE SIGNA® MR system for more detailed warnings regarding safe use of this system.

PRECAUTIONS

- The safety and effectiveness of ExAblate have not been evaluated in women with the following conditions:
  - Pedunculated fibroids
  - Active pelvic disease or infection
  - Undiagnosed vaginal bleeding
  - Uterine size > 24 weeks
  - Weight > 250 pounds
  - Underlying bleeding disorders
  - Previous uterine artery embolization
  - More than one prior ExAblate® 2000 treatment

- The physician should obtain a detailed medical history prior to treatment. Due to the period of immobilization required for the ExAblate treatment, this should include factors that may impact the risk of clotting, and assess the use of measures to minimize the risk of deep venous thrombosis.

- The patient should be instructed to shave all hair from the abdomen prior to the procedure, and the skin should be wiped with alcohol immediately before treatment to remove oils to reduce the risk of skin burns.

- Patient positioning should be optimized at the beginning of treatment to optimize the treatment and to reduce the likelihood of positional pain.

- Restraints may be used to minimize the risk of movement during treatment.

- The patient must be monitored and the level of conscious sedation must be managed appropriately to ensure that the patient can communicate with the doctor throughout the treatment. This allows the patient immediate use of the Stop Sonication Button and/or the ability to immediately inform the doctor of any pain or discomfort during the treatment.

- Thermal feedback from the ExAblate should be used throughout the treatment to plan succeeding sonications. The accuracy of the MR thermal imaging as measured in rabbit muscle is +/-10° C. The accuracy in human fibroid tissue has not been measured. The temperature should be limited to $\leq$ 85° C at the focal point to avoid thermal injury outside the intended treatment volume.

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- Do not attempt to use components other than the ExAblate hardware, software, and system accessories, and the specified MR imaging system with the device.

- Do not attempt to repair the ExAblate System in the event of system failure, malfunction or any evidence of damage to the components. Contact InSightec technical support at **1-866-674-3874**

Refer to the Operator's Manual for both the ExAblate and the GE SIGNA® MR system for more detailed precautions regarding safe use of this system.

ADVERSE EVENTS

The ExAblate was evaluated in a prospective, concurrently controlled, non-randomized clinical trial of 192 patients with uterine fibroids. The ExAblate was compared to a control group treated with total abdominal hysterectomy. A table summarizing all AEs observed in the ExAblate group in this study is presented below (see **Table 1**). Some patients had more than one event in a given time period. The AEs that were most frequently reported (≥ 10% of patients) among ExAblate patients were abdominal pain, "other" pain, nausea/vomiting, and positional back pain.

Table 1 Incidence of Adverse Events in ExAblate Patients in the Pivotal Clinical Study (N=109)

Body System	Adverse Event	n (%)
Pain/Discomfort	Abdominal pain	42 (38.5%)
	Other pain *	14 (12.8%)
	Back pain - positional	11 (10.1%)
	Abdominal tenderness	10 (9.2%)
	Leg pain – sonication related **	8 (7.3%)
	Abdominal cramping	4 (3.7%)
	Back pain – sonication related **	4 (3.7%)
	Discomfort	2 (1.8%)
Gynecological	Abnormal vaginal discharge	10 (9.2%)
	Heavy menses	8 (7.3%)
	Vaginal bleeding	1 (0.9%)
	Abdominal cramping	5 (4.6%)
	Vaginal discharge	1 (0.9%)
Urinary	Urethral pain	8 (7.3%)
	Bladder symptoms	6 (5.5%)
	Increased urinary frequency	6 (5.5%)
	Urinary tract infection	4 (3.7%)
Gastrointestinal	Nausea/vomiting	14 (12.8%)
	Diarrhea	4 (3.7%)
	Constipation	3 (2.8%)
	Flatulence	1 (0.9%)
	Bowel distention	1 (0.9%)
	Bowel symptoms	2 (1.8%)
Systemic	Fatigue	8 (7.3%)
	Discomfort	7 (6.4%)
	Fever	2 (1.8%)
Dermatologic	Skin burn	5 (4.6%)
	Skin redness	4 (3.7%)
	Edema	4 (3.7%)
	Skin irritation	2 (1.8%)
	Firmness	1 (0.9%)
	Scarring	1 (0.9%)

*: This is patient reported pain related to position or other causes.
**: This is patient reported pain that was directly related to the sonication.

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Table 2 Summary of Adverse Events by Body System:

0 – 10 days and 11 days – 6 Months Post ExAblate Treatment

	Test Arm: N=109	
	0 – 10 days	11 days – 6months
Total Number of Adverse Events	271	
Body System	n (%)	n (%)
Pain/discomfort	97 (45.3%)	17 (29.8%)
Gynecological	21 (9.8%)	15 (26.3%)
Urinary	28 (13.1%)	5 (8.8%)
Gastrointestinal	28 (13.1%)	4 (7.0%)
Systemic	15 (7.0%)	8 (14.0%)
Dermatological	16 (7.5%)	5 (8.8%)
Nervous	6 (2.8%)	2 (3.5%)
Cardiovascular	3 (1.4%)	0 (0.0%)
Dental	0 (0.0%)	1 (1.8%)
Other	0 (0.0%)	0 (0.0%)
Total	214 (79%)	57 (21%)

A total of 271 AEs was observed over the 6-months of the Pivotal Study by the ExAblate patients (see **Table 2**). The majority of these events, 79% (214) occurred during the first 10-days post ExAblate treatment, whereas 21% (57) of them occurred thereafter. Of the events that occurred >10 days post-treatment, only 5 events (1.8% of the 271 total number of events) were reported to be severe: 1 event of UTI and 4 events of menses like symptoms.

In addition to the general adverse event information reported above, there are two specific risks of ExAblate treatment that are described in greater detail below: (1) sacral nerve stimulation or injury; and (2) skin burns.

Nerve Stimulation or Injury

A number of patients treated with the ExAblate experienced leg pain or sensations of nerve "tingling" or activation during the treatment process. In most cases, the patient noticed the sensation of lower extremity pain during one or more sonications, and the pain had completely subsided by the day after treatment. However, in a few cases, pain or possible sacral nerve injury persisted beyond this period. This pain was attributed to the heating of the sacral nerves in the far field, which may have resulted from improper beam angulation or failure to maintain the 4 cm minimum distance between the treatment focus and the bone. During treatment planning, these key structures must be identified to minimize/avoid any heating where it may be a potential risk to the patient, e.g., the sacral bundle in the far field of the beam.

Fourteen instances of leg pain were reported among the 109 ExAblate patients, of which 8 were determined to be sonication-related. Of these, 3 were transient, and did not persist after the treatment, and one patient had pain that lasted 2 days. In all but 4 Pivotal Study patients the pain resolved completely by 3 days post-treatment. One patient had long lasting clinically significant effects. This

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patient was 39 years old at the time of her treatment. Immediately after the treatment she reported pain in her left leg and left buttock. At the initial follow-up visit three days later, she reported that the pain had increased, and her left leg was weak. At one month she returned for a scheduled visit and reported significant sciatic pain. A neurological workup indicated damage to the sacral nerve on one side. Over the next several months, she showed progressive improvement and returned to near-baseline status at 11 months post-treatment with full mobility and was pain free.

If pain occurs during a given sonication, the patient herself can instantly terminate the delivery of energy with the Stop Sonication Button. The treatment plan for the succeeding sonication should be reviewed, and if appropriate the treatment location and/or treatment angle immediately adjusted before the treatment continues. If sonication related leg-pain persists, the treatment should be terminated. Continuing interaction between the patient and the physician is important to ensure that any patient sensations of nerve activation are communicated to permit adjustment of the treatment plan as necessary to avoid injury. In addition to leg pain that may be indicative of potential nerve injury, "tingling" of the nerves or similar sensations were sometimes reported in the clinical study for individual sonications. Such sensations may also be indicative of heating of the nerves. Therefore, it is recommended that any report of pain or tingling in the back or leg be thoroughly investigated before proceeding to the next sonication. The treatment plan should be modified as appropriate to reduce this risk (e.g., evaluate the far field beam path to identify nerve location, move or delete sonications in this area, change the tilt of the transducer to move the far field off the nerve, or change the tilt of the transducer to increase the incidence with the sacrum or other bony structures).

Skin Burns

Improper acoustic coupling between the skin and the gel pad can result in undesired heating of the skin due to increased reflection of the ultrasound energy. Examples are air bubbles present in the skin folds and around the hair, or oil between the skin and the gel pad. There were five cases of first or second degree skin burns during the Pivotal Study. In all the cases of skin burns, the patients had hair in the sonication pathway. One patient also moved and decoupled from the acoustic gel resulting in a first degree skin burn.

The following actions are recommended to minimize the occurrence of skin burns:

- Shave all hair from the lower abdomen to two centimeters below the crest of the pubic bone
- Clean the skin on the abdomen with alcohol to remove oil on the skin
- Limit patient movement by using restraints
- Examine the MR planning images for air bubbles at the skin-gel interface and for skin folds prior to sonication

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Other Adverse Events:

No deaths or life-threatening events were observed in the Pivotal Study of the ExAblate. However, as with all thermal ablation procedures, serious injury or death can occur, although these types of events are expected to be rare. The following adverse events could occur, although not observed in the present study:

- Hemorrhage
- Pulmonary embolism (PE)
- Complications of pregnancy
- Damage to organs outside of the uterus
- Sepsis
- Complications leading to serious injury or death

Commercial experience with the ExAblate outside the United States has indicated a similar safety profile to what was observed in the U.S. Pivotal Study. Although one patient treated with a commercial unit outside the United States died from a pulmonary embolism following ExAblate treatment, the death was determined to be unrelated to the device and was attributed to the patient's multiple risk factors, including blood clotting disorders, family history of clots, age > 45, elevated BMI, undiagnosed lung cancer, and a lengthy flight prior to the procedure.

CLINICAL STUDY

Study Objective

The objective of this trial was to evaluate the safety ExAblate in the treatment of uterine fibroids compared to total abdominal hysterectomy, and effectiveness of the ExAblate treatment in reducing pre-treatment symptoms.

Study Hypotheses

Primary Hypothesis

ExAblate treatment would result in an improvement of 10 points from the pre-treatment values in the Symptom Severity Scale (SSS) of the UFS-QOL at 6 months post-treatment in at least 50% of patients, demonstrating that ExAblate is an effective treatment for symptomatic uterine fibroids.

Secondary Hypotheses

- The incidence of Significant Clinical Complications (SCC) would be significantly lower for patients treated with ExAblate (Test Arm patients), demonstrating that ExAblate is a safe treatment for uterine fibroids.

- The trajectory of recovery as measured by repeated assessments of the SF-36 would be more rapid for the ExAblate patients than the hysterectomy patients with equivalent general health states noted at the end of the 6 month follow-up.

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The study endpoints (including endpoints for evaluating the study hypotheses) were:

Primary Effectiveness Endpoint

- Symptom Severity Scale score of the UFS-QOL

Secondary Effectiveness Endpoints

- UFS-QOL subscales
- SF-36
- Overall treatment effect and patient satisfaction
- Fibroid size

Safety Endpoints

- Adverse events (number and distribution of events by type, severity, coded category and incidence per patient)
- Significant Clinical Complications (as described by Dicker RC, Greenspan JR et al, 1982)
- Procedure-related safety data

Study Methodology

This study followed a non-randomized, multi-center, international, concurrent-enrollment design whereby patients were enrolled into one of two parallel treatment arms (ExAblate or hysterectomy). Patients were enrolled in a 3:2 ratio; a total of 192 patients participated in the study (109 ExAblate; 83 hysterectomy). Currently, data are available through 6 months for the entire intent-to-treat population, and for a subset of patients at 12 months, with ongoing data collection at longer follow-up.

Inclusion Criteria

Patients satisfying the following inclusion criteria were eligible for participation in the study:

- Women age 18 years and older who presented with symptomatic uterine fibroids and who had completed their families
- Patients using hormone replacement therapy continued with therapy as before treatment
- Clinically normal Pap smear within timing of national guidelines in the country of the clinical site
- Able and willing to give consent and able to attend all study visits
- Ability to read in either English, French, German, or Hebrew
- Score of 41 or greater on the UFS-QOL Symptom Severity Score
- Patient was pre- or perimenopausal (within 12 months of last menstrual period)
- Able to communicate sensations during the ExAblate procedure

- Uterine fibroids which were device accessible (i.e. positioned in the uterus such that they could be accessed without being shielded by bowel, bladder, or bone)
- Tumor(s) clearly visible on noncontrast MRI
- Use or non-use of hormonal contraception maintained uniformly from 3 months pre-study throughout the 6 month follow-up period

Exclusion Criteria

Patients who met *any* of the following criteria were excluded from the study:

- Uterine size >24 weeks as evaluated by ultrasound or MR
- Patients on dialysis
- Hematocrit < 25%
- Hemolytic anemia
- Previously on GnRH agonist therapy within the 6 months prior to the start of the study
- Unstable cardiac status including:
    - Unstable angina pectoris on medication
    - Documented myocardial infarction within 6 months of protocol entry
    - Congestive heart failure that required medication (other than diuretic)
    - Anti-arrhythmic drugs
    - Severe hypertension (diastolic BP > 100 on medication)
    - Cardiac pacemakers
- Severe cerebrovascular disease [multiple CVAs (cerebrovascular accidents) or CVA within the 6 months prior to the start of the study]
- Anticoagulation therapy or underlying bleeding disorder
- Active pelvic infection or history of pelvic inflammatory disease
- Pelvic mass outside the uterus suggesting other disease processes
- Weight > 250 pounds
- Severe hematological, neurological, or other uncontrolled disease
- Pregnant, as confirmed by serum at time of screening, or urine pregnancy on the day of treatment
- Patients with standard contraindications for MR imaging such as non–MRI-compatible implanted metallic devices
- Known intolerance to the MRI contrast agent (e.g. Gadolinium or Magnevist)
- Individuals who were not able or willing to tolerate the required prolonged stationary prone position during treatment (approximately 3 hours)
- Patients who had an intrauterine contraceptive device anywhere in the treatment beam path
- Extensive abdominal scarring in an area of the abdomen directly anterior to the treatment area
- Patients who were breastfeeding

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Treatment Guidelines

The Pivotal Study was performed under treatment guidelines that were devised to ensure the development of the full safety profile of the ExAblate system in treatments of uterine fibroids. These treatment guideline requirements considerably restricted the area of treatment that could be performed. The treatment guidelines used in the Pivotal Study were as follows:

- The prescribed area intended for treatment could not exceed 33% of the total volume of each fibroid to be treated.
- The treatment plan must maintain a 15 mm margin between the prescribed treatment volume and the serosa or endometrium.
- The prescribed volume could not be closer than 5 mm from the inner portion of the capsule of the fibroid on the side of the fibroid adjacent to the uterine serosa. On the side of the fibroid adjacent to the endometrial cavity, treatment may include the fibroid capsule.
- Up to a total of 4 fibroids could be treated.
- The maximum prescribed volume could not exceed 100 cc for a single fibroid, and 150cc in the case of 2 or more fibroids.
- Only a single treatment was allowed.

Based on recent literature [11], incomplete infarction of uterine fibroids may have the potential for re-growth of residual perfused portions of the fibroid, which may lead to reoccurrence of the fibroid symptoms. Furthermore, during the course of the Pivotal Study, no safety issues related to heating of the endometrium and serosa, or treatment effects outside fibroid capsule were identified. Consequently, for the marketed version of the ExAblate system in the treatment of uterine fibroids, the treatment guidelines have been changed to:

- The maximum volume of an individual fibroid to be sonicated should not exceed 50%
- When targeting a volume of fibroid, ensure that no portion of the targeted volume is within 15 mm of uterine serosa
- A second ExAblate treatment session may be performed within 2 weeks of the first treatment

These treatment guidelines that are described in the labeling ensure patient safety while at the same time providing the ExAblate treatment of uterine fibroids to result in an overall improved symptom relief over a long period of time.

Patient Population

Starting March 2002, 109 patients were treated with ExAblate, and the last 6 month visit of the study ended in June 2003. Eighty-six patients were treated in the hysterectomy arm of the study (see **Table 3**).

Table 3: Patient Disposition Up to 6 Months Post ExAblate Treatment

	Treated		6 Months	
	ExAblate	**Hysterectomy**	**ExAblate**	**Hysterectomy**
Participating	109	83	106 (97.3%)	68 (81.9%)
Withdrew			3	2
Lost To Followup			0	13
Evaluable			95	63
Non-Evaluable *			11	5
Treatment Failures (Alternative Treatment)			4	0

*Patients were non-evaluable due to diagnosis of adenomyosis, baseline UFS-QOL score taken >45 days prior to treatment, no 6-month symptom severity score (SSS), or too few sonications performed. These patients are considered to have had a change in SSS of 0.

Demographic and Other Baseline Characteristics

The mean age of the patient population in both groups was approximately 44 years, which is consistent with a uterine fibroids patient population. There were no statistically significant differences between the groups with regard to age or hormonal status. There were significant differences between the ExAblate and hysterectomy groups with regard to the variables BMI and race. The women in the hysterectomy group had a higher BMI, and while 11% of the ExAblate patients were African-American, 34% of the hysterectomy group was African-American.

Other co-morbid conditions were compared between the treatment and the control groups. Out of the18 recorded conditions, the following were higher in the control vs the treatment group: diabetes mellitus (10% vs 3%); hypertension (24% vs 4%); anemia (11% vs 2 %); and affective disorder (12 % vs 0 %).

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Most patients across both treatment groups had no concurrent gynecological disease (ExAblate group 92%; hysterectomy group 89%). For those patients who reported a gynecological disease, no significant differences between treatment groups in the types of disease were observed.

Baseline/Procedure Information for ExAblate Group:

For patients in the ExAblate group, MR information was available to characterize the location, type, numbers and sizes of the fibroids (see **Table 4**).

Table 4 Summary of Fibroid Information and Characteristics for Patients in the ExAblate Group of the Study

Variable	ExAblate Group (Mean±SD)
Uterine volume (cm^3) (mean±SD) [a]	595.0±362.5
Number of visible fibroids/patient [b]	2.3±2.0
Number of treated fibroids/patient [c]	1.3±0.6
Total # of Treated fibroids	(N=137) *
Location	
Submucosal (n)	28
Intramural (n)	81
Subserosal (n)	24
Undetermined (n)	4
Total (n)	137
Volume of sum of slices (cm^3) [d]	284.7±225.4
Region of treatment (cm^3) [e]	25.6±18.4
Thermal dose volume (cm^3) [e]	25.5±18.2
Nonperfused volume (cm^3) [f]	62.4±70.4
Total Fibroid Load (at Baseline) (cm^3) [c]	372±235

a: 106 patients b: 99 patients c: 102 patients
d: 98 patients e: 100 patients f: 101 patients
* Number of fibroids with Core Lab data

Seventy-one patients (69%) had one fibroid treated while 32 patients (31%) had multiple (up to four) fibroids treated.

Primary Study Hypothesis (Effectiveness Evaluation)

The primary hypothesis was evaluated using the primary effectiveness endpoint of the study, the Symptom Severity Score subscale of the Uterine Fibroid Symptom Quality of Life (UFS-QOL) questionnaire. This instrument has been validated specifically for use in uterine fibroid patients. The Symptom Severity Score includes a series of questions related to the predominant uterine fibroid symptoms of bulk and bleeding. A 10-point improvement in the SSS was defined as clinically significant. **Table 5, Figure 5,** and **Table 6** show the score changes on this scale for the 109 subjects in the ExAblate group; this includes patients

who withdrew, were lost to follow-up, or who were treated outside of the protocol limitations, all of whom were counted as failures. The data are also presented for the 95 subjects who were deemed "evaluable" (i.e., treated within all specifications of the study protocol). The SSS evaluation was not relevant to the hysterectomy group, because these patients no longer had fibroid-related symptoms once their uterus was removed.

Table 5 Analysis Mean Change Score: Symptom Severity – ExAblate Group at 6 Months

Symptom Severity Score	Baseline Mean (SD)	Month 6 Mean (SD)	Mean Change Score (SD)	Change Range	*P*-value
ExAblate Group (N=109)	61.1.0 (16.3)	37.3 (21.4)	-23.8 (21.2)	-81.3 to 18.8	<0.0001
Evaluable (N=95)	61.6 (14.9)	37.9 (21.2)	-23.7 (21.4)	-81.3 to 18.8	<0.0001

Note: A higher Symptom Severity Score indicates a higher level of symptom severity.

Figure 5 Intent-to-Treat Distribution in Reduction in Symptom Severity Scores for ExAblate Treated Patients at 6-Months (higher score indicates greater reduction in symptoms)

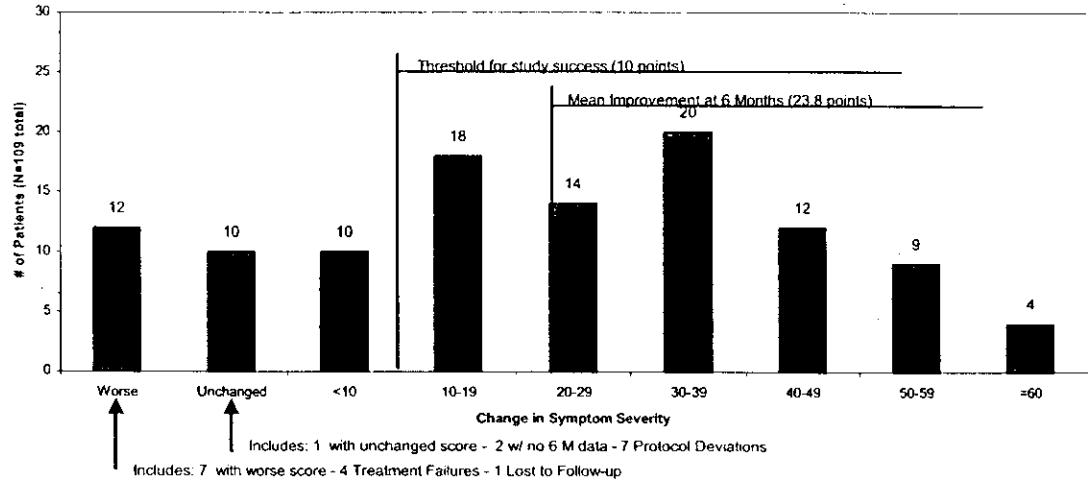

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Table 6 Success Rate For Month 6 Based on Original Intent to Treat Population	N=109
≥ 10 Point Improvement: Baseline -> 6M	77 (70.6%)
Unchanged or Worsened patients: Baseline -> 6M – All Patients	32 (29.4%)
Success Rate For Month 6 Based on Evaluable Patient Population	**N=95**
≥ 10 Point Improvement: Baseline -> 6M	67 (70.5%)
Unchanged or Worsened patients: Baseline -> 6M – All Patients	28 (29.5%)

Study success was based on at least 50% of the ExAblate group population attaining a 10-point improvement on the SSS at 6 months. The result of this study showed that 70.6% of all ExAblate patients achieved a 10-point change at 6 months.

The majority of the symptom improvement was observed at 3 months post-treatment; however, there was continued evidence of slight improvement between 3 and 6 months.

Secondary Effectiveness Endpoints

In addition to the Symptom Severity Score, the UFS-QOL includes a number of other health-related quality of life subscales, including level of concern regarding symptoms, impact of symptoms on activities, energy/mood, control over one's life, feeling self-conscious, and sexual function. These scales all showed similar improvement trends.

SF-36 Quality of Life Results

The SF-36, a general health survey instrument, was administered as a comparator between the ExAblate and hysterectomy groups. The results of the SF-36 generally showed a significant advantage in favor of the ExAblate Group at one month due to the significant disability resulting from hysterectomy. Both groups showed significant improvement at 3 and 6 months compared to Baseline, although there were some aspects of the SF-36 in which there was an advantage for the hysterectomy group at 6 months.

By Month 3, ExAblate Group patients still had generally higher scores than hysterectomy patients in the areas of physical function, role-physical, and role-emotional, although these differences were not statistically significant. Significant differences were present, however, between the ExAblate and hysterectomy groups in the bodily pain and mental health subscales, favoring hysterectomy patients. At Month 6, the hysterectomy group reported significantly higher scores than ExAblate Group in role-physical, bodily pain, general health, vitality and mental health; while no differences were noted in the other subscales. These differences may be related to the fact that while patients in the ExAblate group experienced a significant improvement in their fibroid QOL scores versus

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Baseline, by retaining their uteruses, they continued to experience pain, fatigue, and premenstrual tension anxiety related to their continuing menstruation.

Overall Treatment Effect and Patient Satisfaction

In addition, a two-part "Overall Treatment Effect" questionnaire was administered to solicit the patient's general opinion on the outcome. The results demonstrated that the majority of both the ExAblate and hysterectomy groups felt that they had improved and were satisfied with the treatments, although the degree of relief in the hysterectomy group was more complete.

At the 6 month visit, patients were asked for their general impression of the treatment. The results from 102 patients who responded were as shown in **Table 7**.

Table 7 ExAblate Patient Satisfaction Results at 6-Months

	N = 102
Were you satisfied with your treatment?	76% Satisfied
How effective was this treatment in eliminating your symptoms?	72% Effective
Would you recommend this to a friend with same health problem?	84% Would Recommend

Fibroid Shrinkage

MRI images prior to treatment and at 6 months were compared to determine fibroid shrinkage. This is shown in **Table 8**. MR images were available for review on 102 patients.

Table 8 Fibroid Shrinkage

Parameter	**N = 102**
Baseline Volume of Treated Fibroids (cm^3)	334.4 ± 240.4
6 month Volume of Treated Fibroids (cm^3)	295.4 ± 256.4
6 month % Shrinkage of Treated Fibroids	15.3 % ± 30.4%

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Safety Evaluation

Significant Clinical Complications (SCCs)

SCCs, which were the basis for evaluating one of the secondary study hypotheses, are summarized in **Table 9**.

Table 9 Incidence of Significant Complications in the Pivotal Clinical Study: ExAblate Group and Hysterectomy Group

	ExAblate Group (N=109)	Hysterectomy Group (N=83)
Number of patients with at least 1 Significant Clinical Complication	**13 (12%)**	**38 (46%)**
Re-hospitalization duration > 24 hours	8	8
Fever > 38°C on any 2 post-treatment days (excluding first 24 hours)	3	12
Antibiotic use starting > 24 hours post-treatment	3	30
Transfusion	3	6
Unintended surgical procedure related to treatment	0	4
Referral to a rehabilitation facility	0	0
Discharge with appliance	0	1
Life-threatening event	0	0
Interventional treatment	0	2
Death	0	0
Total number of occurrences	**17**	**63**

It is problematic to draw conclusions regarding the relative safety of the two procedures because of significant differences in baseline health of the two study arms.

Trajectory of Recovery

Data with respect to disability days demonstrated the recovery pattern of the ExAblate patients. At the Month 1 visit, patients in the ExAblate group reported an average of 1.2 disability days, compared to 19.2 days in the hysterectomy group.

Patients who were treated by ExAblate required 84% fewer provider encounters, and 66% fewer additional procedures compared to the hysterectomy group.

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Anesthesia Regimen and Dosage

The anesthesia requirements for this treatment are similar to other minimally invasive procedures. The level of sedation/analgesia should be based on patient response. Patients should be kept comfortable, but able to fully respond and participate in the treatment. The rapid recovery time discussed above is attributable to the fact that patients can be treated with the ExAblate under conscious sedation rather than general anesthesia.

LONG TERM MONTH 12 FOLLOW-UP STUDY

A long-term follow-up plan to obtain safety and efficacy data has been developed. The long term follow-up study is being conducted by the same sites and the same investigators as the original treatment study. **Table 10** shows the disposition of all patients initially enrolled in the study until 12 months.

Table 10: Patient Disposition Up To 12 Months Post ExAblate Treatment

	Treated		0-6 Months		6-12 Months	
	ExAblate	Hysterectomy	ExAblate	Hysterectomy	ExAblate	Hysterectomy
Participating	109	83	106 (97.3%)	68 (81.9%)	91 (83.5%)	N/A
Withdrew			3	2	0	
Lost to Follow-Up			0	13	6	
Declined Participation*			0	0	9	
Evaluable			95	63	82	
Non-Evaluable **			11	5	9	
Treatment Failures (Alternative Treatment)			4	0	23	

*These patients were contacted but declined to return for follow-up at 12 months. The study and the patients' consent had initially been limited to 6 months.

**Patients were non-evaluable due to diagnosis of adenomyosis, baseline UFS-QOL score taken >45 days prior to treatment, no symptom severity score (SSS), or too few sonications. These patients are considered to have had a change in SSS of 0.

Evaluation of Effectiveness for Patients in the 12-Month Long Term Follow-Up Study

Figure 6 and **Table 11** show the score changes on the SSS scale for the 109 subjects in the ExAblate group; this includes patients who withdrew, were lost to follow-up, or who were treated outside of the protocol limitations, all of whom were counted as failures.

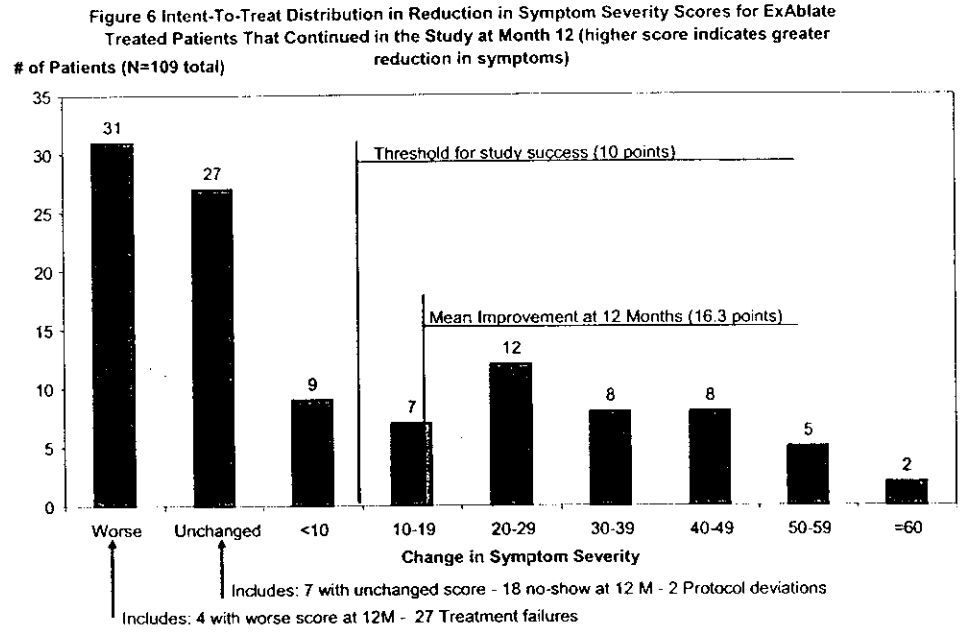

Table 11: UFS-QOL Subscale Symptom Severity Score	
Success Rate For Month 12 Based on Original Intent to Treat Population	**(N= 109)**
≥ 10 Point Improvement: Baseline to > 12 months	42 (38.5%)
Unchanged or Worsened patients: Baseline to > 12 months	67 (61.1%)
Success Rate For Month 12 Based on Patients Participating in 12-Month Visit	**(N=82)**
≥ 10 Point Improvement: Baseline to > 12 months	42 (51.2%)
Unchanged or Worsened patients: Baseline to > 12-months 12M	40 (48.8%)

Table 11 shows the success rate for Month 12 based on both the original treatment population (N=109) and the participating patients (N=82). Of the original treatment population of 109 patients, 38.5% of these patients had ≥ 10

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points improvement from baseline. There were 51.2% participating patients that had ≥10 points improvement from baseline.

At the 12 month point, 21% (23) of the original ExAblate patients had chosen to go on to additional surgical treatments; four had undergone a second ExAblate treatment.

12-Month Safety

There were no occurrences of other adverse events between 6- and 12-months post-ExAblate. For patients in the ExAblate group, throughout the 12 months post-treatment period, there were no device-related deaths, life-threatening injuries or permanent injuries, acute hospitalizations, or device-related emergency interventional procedures.